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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,418	05/13/2005	Edouard S.P. Bouvier	60009US(49991)	4955
48990 7590 03/17/2010 EDWARDS ANGELL PALMER & DODGE LLP P.O. BOX 55874 BOSTON, MA 02205				
EXAMINER ARNOLD, ERNST V				
ART UNIT		PAPER NUMBER		
1616				
MAIL DATE		DELIVERY MODE		
03/17/2010		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/516,418

Applicant(s)

BOUVIER ET AL.

Examiner

ERNST V. ARNOLD

Art Unit

1616

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12/17/09.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 124-139 and 141-150 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 124-139 and 141-150 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB-06)
Paper No(s)/Mail Date _____

- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Claims 1-123 and 140 have been cancelled. Claim 151 has been withdrawn.
Claims 124-139 and 141-150 are under examination.

Withdrawn rejections:

Applicant's amendments and arguments filed 12/17/09 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn. Claims 124-142, 144-147, and 150 were rejected under 35 U.S.C. 102(a) as being anticipated by Zeller et al. (Journal of Biomolecular Techniques 2002, 13(1), 1-4). Zeller does not disclose degrading the surfactant after the chemical digestion.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 124-139 and 141-150 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (WO 00/70334) in view of Zee-Yong et al. (Anal Chem. 2001, 73, 2558-2564) and Nelson (US 6,093,541) and Meng et al. (Anal Chem 2002, 74, 2923-2929; published on the Web 5/9/2002).

Applicant claims:

124. (Currently Amended) A method for enhancing chemical digestion of a biomolecule comprising contacting the biomolecule with (i) a protease, CNBr or hydroxylamine and (ii) a surfactant represented by formula I:



in which

p is 0, 1 or 2;

R is alkyl;

R₂ and R₃ are each, independently, hydrogen or methyl; and

R₁ is selected from -OSO₃⁻, -R₄OSO₃⁻, -R₄OR₅SO₃⁻, and -OR₅NO₂⁻,

wherein R₄ and R₅ are each, independently, lower alkyl; and

wherein the biomolecule is selected from the group consisting of a protein and a peptide; and

wherein the activity of said protease, CNBr or hydroxylamine is maintained or increased upon contact with the surfactant;

thereby enhancing the chemical digestion of said biomolecule;

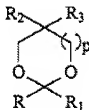
wherein the surfactant is degraded after the chemical digestion.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Lee et al. teach in claim 27:

27. A method of solubilizing a substance comprising contacting a substance with a surfactant represented by the formula (Formula I):



in which

p is 0, 1 or 2;

R is alkyl;

R₁ and R₂ are each, independently, hydrogen or methyl; and

R₃ is selected from -OSO₃⁻, -R₄OSO₃⁻, -R₄OR₅SO₃⁻, and -OR₅SO₃⁻,

wherein R₄ and R₅ are each, independently, lower alkyl.

Instant claim 142 is taught when R₂ = H and p = 0. Instant claim 143 is obvious when p = 1, R₂ = H, R₃ = -OR₅SO₃⁻, R = alkyl and R₁ is methyl (Page 12, Scheme 1). Instant claim 144 is taught when p = 0, R₁ = methyl, R = alkyl, R₂ = H and R₃ = -R₄OSO₃⁻ (Page 12, Scheme 1). Lee et al. teach wherein the substance is an inclusion body, lipophilic protein or membrane-bound protein sample (Claims 28-31). Lee et al. teach a method where a proteolytic protein (lysozyme, trypsinogen, pepsin, for example) is contacted with ALS-I (page 14, lines 5-15). Therefore, it is

the position of the Examiner that contacting enzymes with the surfactant is taught in the art. The presence of a biomolecule in the aqueous surfactant solution makes it a biological sample. The aqueous surfactant solution has water, which is a biological fluid. Samples were heated to ensure protein denaturation (page 14, lines 14-15). Gels were run in the absence of SDS (page 14, lines 26-31). Lee et al. teach 50 μ L aliquots and thus perform under microscale conditions. Mass spectrometry was used for detection of myoglobin treated with ALS-I (page 15, lines 4-22). Lee et al. state that “mass spectrometric detection” refers to Matrix Assisted Laser Desorption Ionization MALDI which applicant states on page 21 lines 21-22 is surface desorption ionization analysis (Page 6, lines 30-32). Gels run with ALS-I were stained with zinc-imidazole (page 14, lines 26-31). On one hand, the surfactant was degraded in glacial acetic acid for 16 prior to mixing with myoglobin and on the other hand trifluoroacetic acid was added to degrade the surfactant before electrospray mass spectrometry of myoglobin (page 15, lines 10-22; page 16, line 8 and page 18, lines 14-26). Therefore, Lee et al. is directed to performing mass spectrometry on biomolecules using the acid labile surfactant.

Zee-Yong et al. teach identification of individual proteins (11 proteins were studied and include: rabbit phosphorylase, bovine serum albumin, chicken egg ovalbumin, rabbit aldolase, bovine carbonic anhydrase, horse myoglobin, bovine hemoglobin, horse cytochrome c, chicken egg lysozyme, and bovine ubiquitin (Page 2559 Experimental section).) in complex protein mixtures by MALDI mass spectrometry (Abstract). Thermal denaturation followed by in-solution trypsin digestion is used to achieve uniform digestion of the constituents of the protein mixture (Abstract and page 2559, experimental section). **Reduction** of disulfide bonds with dithiothreitol is taught (page 2559, right column).

Nelson teaches proteases for use in mass spectrometers (Abstract and column 7, lines 28-65 and claim 4). Nelson teaches chymotrypsin, Glu-C, Lys-C, *S. aureus* V8 protease, clostripain, and trypsin, for example, as enzyme proteases and chemical agents such as cyanogens bromide and hydroxylamine (column 7, lines 28-65). Nelson teaches immobilized proteases (Figures 3, 3A, 5 and 6; and column 16, example 10 for example). Nelson teaches adding **reducing agents** (column 7, lines 55-57).

Meng et al. establish that it was known in the art to use acid labile surfactants of the instant structure and demonstrated 1D ALS-PAGE along with sensitivity enhancements for peptide mapping after *in-gel digestion* (Abstract; page 2924, chart 1 and left column and Experimental Section). *Thus, enhanced digestion using acid labile surfactants is a concept already known in the art.*

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. Lee et al. do not expressly teach a method for enhancing chemical digestion of a biomolecule comprising contacting the biomolecule with a protease, CNBr or hydroxylamine and a surfactant whereby the activity of the protease, CNBr or hydroxylamine is maintained or enhanced and the surfactant is degraded after the chemical digestion. This deficiency in Lee et al. is cured by the teachings of Nelson et al. and Zee-Yong et al. and Meng et al.

2. Lee et al. do not expressly teach a method that is performed in the presence of SDS or one or more other surfactants. This deficiency in Lee et al. is cured by the teachings of Zee-Yong et al. and Meng et al.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform a method for enhancing chemical digestion of a biomolecule comprising contacting the biomolecule with a protease, CNBr or hydroxylamine and a surfactant or contact the biomolecule with a protease that is immobilized and degrading the surfactant after the chemical digestion, as suggested by Zee-Yong et al. and Nelson and Meng et al., in the method of Lee et al. and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Lee et al. is directed to mass spectrometry of biomolecules and Zee-Yong et al., Meng et al., and Nelson teach common reagents and techniques known to one of ordinary skill in the art of protein mass spectrometry. The resulting enhancements would be intrinsic to the method. With respect to degrading the surfactant after digestion, Lee et al. teach in one example that degradation of the surfactant is required for detection of myoglobin (page 18, example 7). Accordingly, one of ordinary skill in the art would degrade the surfactant after chemical digestion and before MS analysis.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to perform the method of Lee et al. in the presence of SDS or one or more other surfactants and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because using surfactants such as SDS is commonly done in the art and the acid labile surfactant is known to be

a milder denaturant than SDS (see Meng et al. page 3, results) which required further denaturation by heating. The addition of the known denaturant such as SDS to assist denaturation would avoid heating the sample.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments:

Applicant's asserts that nothing in Lee, Zee Yong, Nelson and Meng teach or suggest the instantly claimed method and that a physical change, solubilization, does not involve a chemical alteration such as digestion, alkylation or reduction of a molecule. It is correct that Lee does not teach digestion, alkylation or reduction of a molecule. As stated above, Lee teaches solubilization of proteins, peptides and proteases (page 5, lines 31-33 and page 14, lines 5-15). Applicant asserts that nothing in Lee would have lead one of ordinary skill in the art to reasonably expect the enhancement of a chemical property of the alkylation or reduction reaction using these surfactants. Respectfully, the Examiner cannot agree because instant claims 124 and

126 only require the activity of the protease, CNBr or hydroxylamine to be maintained. If that is true then the enhancement comes in the solubilization of the protein which Lee teaches. Lee teaches that the surfactants can be used in other applications that can benefit from the initial presence and ultimate removal of a surfactant including solubilization, analysis, separation, purification, and/or characterization of large molecules (page 5, lines 15-18).

Protein digestion before analysis by mass spectrometry is a common procedure known to the artisan of ordinary skill in the art of protein biochemistry that is part of the characterization of large molecules. There is nothing of record that would teach away or suggest that the digestion could not be performed in the presence of the surfactant with the reasonable expectation that the protease would function as a protease. This is especially true when one considers that the ALS is solubilizing both the protein and the protease which would be required for efficient digestion. In fact, Lee et al. teach contacting both proteases and proteins with the ALS and therefore one of ordinary skill in the art would have a reasonable expectation of success in combining the ALS, protease and protein for chemical digestion and expect each component to function normally. Although Lee et al. did not exemplify such a teaching, it is nevertheless within the ordinary artisan's skill to extrapolate the teachings of Lee et al. to include digestion of the protein. Indeed, Lee et al. teach that routine experimentation can ascertain other equivalents to the disclosure (page 21, lines 9-12) and protein digestion is a common procedure in the art. Furthermore, the principle of law states that the obviousness analysis "can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 418 (2007).

Applicant asserts that Meng does not cure the deficiency in Lee. The Examiner is relying on Meng not for the solubilization of intact proteins but for teaching that it was known in the art to use acid labile surfactants of the instant structure and demonstrated 1D ALS-PAGE along with sensitivity enhancements for peptide mapping after in-gel digestion.

Therefore, it remains that Examiner's position that it is obvious to one of ordinary skill in the art of protein biochemistry to use the method of Lee for protein digestion, alkylation or reduction and have a reasonable expectation of success and produce the instant invention. In other words, one would expect the activity of the protease, CNBr or hydroxylamine to be normal.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 124-139 and 141-150 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 13-17 and 19, of US 7,229,539. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant method of enhancing a chemical reaction of a molecule comprising contacting the molecule with a surfactant is encompassed by the patented claims drawn to a method for performing electrophoresis comprising contacting a sample with the same surfactant as instantly claimed as well as the method of solubilizing a substance comprising contacting the substance with the same surfactant as instantly claimed (patented claims 1 and 19). Patented claim 19 recites inclusion bodies, lipophilic proteins, receptors, membrane bound proteins and biological tissues.

The patented claims do not teach the enhancement features that are instantly claimed but such features are intrinsic to the method because the same surfactant is being utilized. The patented claims do not teach performing the method in the presence of SDS or other surfactants but adding one or more surfactants including SDS to assist in denaturation of a biomolecule is nothing more than judicious selection of known surfactants to one of ordinary skill in the art of mass spectrometry of biomolecules.

Therefore, one of ordinary skill in the art would have recognized the obvious variation between the instant invention and the pending application because the subject matter of the instant invention embraces or is embraced by the patented claims.

Response to arguments:

Applicant stated that the rejection would be addressed once allowable subject matter was indicated. Until that time, the claims remain rejected.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (7:15 am-8:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ernst V Arnold/

Primary Examiner, Art Unit 1616